

REMARKS

Claims 2-4, 7, 8 and 12-26 have been cancelled, and claims 1, 5-6, and 9-11 have been amended to more definitely set forth the invention and obviate the rejections. Support for the amendment of claim 1 can be found in original claims 2, 4, 7 and 8, as well as on page 6, lines 14-16, of the Specification. This amendment is deemed not to add new matter. Claims 1, 5-6 and 9-11 remain in the application.

Reconsideration is respectfully requested of the rejection of claims 1-6, 11-15 and 20-26 under 35 U.S.C. 102(b), as being anticipated by Higo, et al. (USPN 5,866,157).

The cited Higo, et al. reference discloses a matrix-type formulation containing organic acid and a basic drug. However, in contrast to the present invention, neither the organic acid, nor the organic acid salt, is an essential element of the formulation thereof. Further, Higo, et al. discloses neither an **acid addition salt of a basic drug** (as now claimed herein in amended claim 1), nor the ratio of the acid addition salt of the acid addition salt of the basic drug to the organic acid salt (i.e., 5:1 to 1:5), as the Examiner has recognized on page 3, fifth paragraph, of the instant Office Action.

To more clearly distinguish from the cited Higo, et al. reference, Claim 1 has been amended herein to more clearly

indicate that all 3 of the claimed elements, i.e., the acid addition salt of a basic drug, the organic acid and the organic acid salt, are essential components, to call for **an acid addition salt** of the basic drug (which is stated to be preferable in the Specification, page 6, lines 14-16), and to require that the ratio of the acid addition salt of the acid addition salt of the basic drug to the organic acid salt be within a range of from 5:1 to 1:5. It is believed that Higo, et al. fail to disclose any of the elements discussed above, which are now claimed herein in amended claim 1.

The purpose of the present invention is to improve the solubility of the basic drug in the matrix-type patch composition which contains no water, by forming ion pairs between the basic drug and the organic acid salt in the matrix-type patch formulation. In particular, it was unexpectedly discovered that inclusion of specified amounts of an organic acid **AND** an organic acid salt into the matrix-type patch formulation, along with a basic drug in the form of an acid addition salt, in the absence of water and in the claimed ratios, provides more stable ion pair formation than in a patch including the organic acid salt alone. A quasi-stable state is obtained from this claimed combination, which is capable of elevating skin permeability of the drug therein (see Specification, page 5, lines 17-27).

Importantly, it is stated that "[t]he ratio of the acid addition salt of the basic drug to the organic acid, when they are compounded, preferably ranges from 5:1 to 1:5 (by equivalent ratio). If the ratio of the acid addition salt of the basic drug is out of the range from 5:1 to 1:5, both stability and skin permeability will be reduced" (see Specification, page 9, lines 2-7). This combination of claimed elements in the claimed ratios constitutes an important element or aspect of the present invention, and is not disclosed in the cited Higo, et al. reference.

In view of the amendments to claim 1 herein, the deficiencies of the cited Higo, et al. reference pointed out above, and the arguments presented herein, it is believed that the Examiner would now be justified in no longer maintaining the rejection. Withdrawal of the rejection is accordingly respectfully requested.

Reconsideration is respectfully requested of the rejection of claims 1-26 under 35 U.S.C. §103(a) as being unpatentable over Higo, et al. (WO 96/16642) in view of Chono, et al. (WO 97/42952).

The cited Higo, et al. reference is discussed above.

It is believed that the cited secondary Chono, et al. reference was cited by the Examiner merely to provide the ratio of the basic drug (in Chono, et al., fentanyl) to organic acid

salt (in Chono, et al., sodium acetate). It is further believed that this reference, like the Higo, et al. reference discussed above, does not require an acid addition salt of a basic drug, an organic acid salt AND an organic acid, as now claimed herein.

With respect to the claimed proportions and ranges of concentrations claimed herein, if the proportions are critical to the properties of the novel product, they can render the product patentable even though the percentages of ingredients fall within the broad ranges of the prior art. *Becket v. Coe* 98 F2d 332, 38 USPQ 26 (CADC 1938); *In re Becket, et al.* 88 F2d 684, 33 USPQ 33 (CCPA 1937); *In re Arness* 95 F2d 344, 37 USPQ 217 (CCPA 1938). The fact that the percentages of the chemical components of a chemical compound fall within the general proportions of the reference does not preclude patentability where the disclosure of the specification is persuasive of the criticality of the claimed proportions. *Ex parte Selby* 153 USPQ 476 (POBA 1966); *In re Waymouth, et al.* 499 F2d 1273, 182 USPQ 290 (CCPA 1974).

In the present invention, Examples 1-6 were prepared comprising the matrix-type patch formulation of the present invention (i.e., a basic drug, an organic acid AND an organic acid salt, in the claimed ratios and concentrations). In addition, Comparative Examples 1-10 were prepared, Comparative Examples 1-6 containing only a basic drug and an organic acid,

and Comparative Examples 7-10, which contained only a basic drug and an organic acid salt.

Each of these compositions was then tested to determine its crystallization (which alters the release characteristics and adhesive properties of a composition) and the percutaneous absorbability. The results of these tests are shown in Table 1, on page 24 of the Specification.

As illustrated in Table 1, it was unexpectedly discovered that by combining the basic drug, an organic acid and an organic acid salt in the claimed ratios and weight ranges, excellent percutaneous absorption, as well as formulation stability, was obtained, perhaps due to the synergistic effect of the claimed combination. In contrast, the present inventors unexpectedly discovered that, as shown in Comparative Examples 1-6, when omitting an organic acid salt, and as shown in Comparative Examples 7-10, when omitting an organic acid, overall poor results are obtained with regards to percutaneous absorption and formulation stability.

Proof of unobviousness of a therapeutically active mixture of compounds can be based on (1) broader therapeutic spectrum, (2) higher activity, (3) more extended of complete activity, (4) improved tolerance, (5) **improved absorption**, (6) decreased toxicity, (7) **reduced sensitization**, (8) elimination of microbial

resistance. Roditi, H. and Bossard, J. "The Patentability of Synergistic Association", 47 JPOS 40, 46-50 (1965).

It is maintained that the unexpectedly superior test results shown in Table 1 illustrate the criticality and unobviousness of the claimed proportions and ranges of the components of the present invention. Based on the teachings of the legal authorities cited above, it is thus believed that these showings clearly demonstrate unobviousness and patentability.

In view of the amendments to the claims herein, the arguments and discussions presented herewith, and the legal authorities cited above, it is believed that the Examiner would now be justified in no longer maintaining the rejection. Withdrawal of the rejection is accordingly respectfully requested.

In view of the foregoing, it is respectfully submitted that the application is now in condition for allowance, and early action and allowance thereof is accordingly respectfully requested. In the event there is any reason why the application cannot be allowed at the present time, it is respectfully requested that the Examiner contact the undersigned at the number listed below to resolve any problems.

Respectfully submitted,

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On Tuesday, October 14, 2003.

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